REMARKS

I. Amendments

Claims 16, 22 and 26 have been amended. Specifically, claim 16 has been amended to depend upon claims 1-10 to provide that the claimed pharmaceutical formulation further comprises a bile acid binder. Claim 22 has been amended to depend upon method claim 16 to provide that the claimed method of treatment further comprises administering a bile acid binder. Claim 26 has been amended to clarify that the pharmaceutical formulation of claims 1-10 is administered in accordance with the claimed method. Support for amended claims 16, 22 and 26 is found in the specification on page 5, lines 11-13. Claim 27 has been canceled.

New claim 28 is directed to an embodiment of the invention deleted from amended claim 16, and is supported by the specification at page 5, lines 11-13. New claim 29 is directed to a combination of claims 16 and 19, and is supported by the specification at page 5, lines 19-21. Claims 30-32 are more particular embodiments of claim 29 and are supported by claims 16, 17, and 18. New claim 33 is directed to a pharmaceutical composition which releases an IBAT inhibitor compound in the ileum and a bile acid binder in the colon, and is supported by the specification at page 14, lines 4-7. New claims 34 and 35 are directed to a method of treatment comprising administering the formulation of claims 29-33 and are supported by the specification and claims, as originally filed.

No new matter is introduced by any of the amendments herein.

II. The claimed invention

The claimed invention is directed to the treatment of hypercholesterolemia comprising administration of an inhibitor compound of the ileal bile acid transport system (IBAT inhibitor compound). Advantageously, the claimed pharmaceutical formulation is constructed in such a

way to obtain the targeted release of the active ingredient directly or close to the site of action, e.g., the ileum. As a result, the IBAT inhibitor is utilized more efficiently, thereby enhancing the cholesterol lowering effect of the drug and reducing undesirable systemic effects on other organs, such as the liver and kidney.

Although administration of the IBAT inhibitor will provide the desired hypocholesterolemic effect, a resultant side effect may be an excess of bile acids in the intestine, resulting in symptoms such as diarrhea. Accordingly, in another embodiment of the claimed invention, the pharmaceutical formulation further comprises a bile acid binder. The bile acid binder absorbs excess bile acids caused by the activity of the IBAT inhibitor and the resulting accumulation of excess bile acids in the colon. The bile acid binder is not included in the formulation to provide additive or synergistic hypocholesterolemic properties. The formulation may be formulated for targeted release of the binder in the colon in order to increase efficacy of the composition.

III. Restriction Requirement

A restriction requirement under 35 U.S.C. § 121 was issued in the subject application. It is alleged that the subject application contained the following inventions or groups of invention which are independent and patentably distinct:

Group I, claims 22 and 27, drawn to a method of treating diarrhea with an IBAT inhibitor; and

Group II, claims 1-10, 15-19, and 24-26, drawn to a formulation comprising an IBAT inhibitor and a carrier, and a method for treating hypercholesterolemia.

Applicants confirm the provisional election of Group II for examination. Applicants submit that the subject matter of new claims 28-35 reads upon the subject matter of elected Group II.

With specific regard to non-elected group I, Claim 27 of Group I has been canceled. Furthermore, claim 22 of Group I has been amended to depend upon claim 15 of elected Group I. Accordingly, withdrawal of the restriction requirement with respect to claim 22 is respectfully requested.

Applicants respectfully submit that the pending claims are directed to a pharmaceutical formulation comprising an IBAT inhibitor compound to be administered in the treatment of hypercholesterolemia. The claimed formulation may further comprise a bile acid binder to be administered in the treatment of diarrhea resulting from an excess of bile acids due to the activity of the IBAT inhibitor compound in blocking the ileal bile acid transport system. Therefore, in accordance with the claimed invention, the indication "diarrhea" is directly related to the possible consequences resulting from the administration of an IBAT inhibitor compound. Accordingly, all of the pending claims 1-10, 15, 16-19, 22, 24-26 and 28-35 should be examined in the same application.

Applicants reserve the right to file a continuation application directed to the subject matter of any canceled claims.

IV. Rejection under 35 U.S.C. § 103(a)

Claims 1-10, 15-19, and 24-26 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over US 5,723,458 to Brieaddy et al. ("Brieaddy") in view of US 5,614,220 to Hirakawa et al. ("Hawakawa") and US 5,659,027 to Spielvogel et al. ("Spielvogel"). The

Examiner alleges that one of ordinary skill in the art would have been motivated to combine the compounds of either Brieaddy or Spielvogel with the formulation of Hirakawa in order to inhibit bile uptake in the intestinal tract, specifically the ileum and colon. Applicants submit the claimed invention is not obvious in view of the cited prior art.

A. Brieaddy and Hirakawa

Brieaddy discloses benzothiazepine compounds which are reported to be useful for inhibition of bile acid uptake (Abstract). As already acknowledged by the Examiner, Brieaddy does not teach the specific release locations of the active ingredient as recited by the claimed invention. Admittedly, therefore, Brieaddy does not suggest the desirability and advantages of a targeted release formulation comprising a hypolipidemic compound for the targeted delivery of the active ingredient in the ileum to enhance the cholesterol lowering effects of the drug and lower the risk of harmful side effects to other organs.

Accordingly, the Examiner relies upon Hirakawa for an alleged disclosure of a pharmaceutical formulation specifically targeted for the digestive tract. Hirakawa is directed to a targeted release formulation comprising a core material, a subcoat applied to the core material, and an enteric coating applied to the subcoat. In accordance with the specification and Examples of Hirakawa, the core material contains and the method of treatment consists of the administration of only one medicinal active ingredient (See, claim 1). Concrete examples of such medicinal active ingredients include a broad range of disparate agents such as chemotherapeutics, psychotropics, hypnotics and antilipemics (See col. 4, lines 24-37). At column 4, lines 14-17 of Hirakawa, it is disclosed that a pharmaceutical formulation can be obtained wherein release of the medicinal active ingredient occurs at the lower ileum, the ascending colon or the transverse colon.

Applicants clarify that although the Examiner is correct in stating that Hirakawa mentions "agents affecting digestive organs" (col. 4, line 31), Applicants' invention is directed to treating hyperlipidemia, which is not a disease or condition of a digestive organ, but rather a lipid imbalance in the blood.

Applicants submit, however, that the Examiner's reliance upon Hirakawa is misplaced. Although Hirakawa includes antilipemic agents (col. 4, line 35) as a possible general class of medicinal active ingredients, this disclosure does not teach IBAT inhibitor compounds, nor does it provide a reasonable expectation of success that IBAT inhibitor compounds may be formulated to provide targeted release of the active agent in the ileum. In this regard, it is noted that none of the working Examples of Hirakawa are directed to targeted release formulations comprising either an antilipemic agent or an IBAT inhibitor compound. Rather, Hirakawa only provides a general disclosure of a laundry list of active agents which one may try to use. There is no suggestion to select IBAT inhibitor compounds from all possible antilipemic agents.

Applicants respectfully submit, therefore, that the Examiner is improperly relying on an "obvious to try" standard with the benefit of a hindsight reconstruction of the claimed invention. However, "obvious to try" is not a proper basis for a §103 rejection when there is no suggestion in the prior art that would have led the skilled artisan to develop a formulation comprising an IBAT inhibitor and, in accordance with certain embodiments, a bile acid binder agent which provides a targeted delivery of the active ingredients.

Specifically, there is no suggestion in Brieaddy or Hirakawa, whether taken alone or in combination, to prepare the claimed targeted release formulations. At the time of the claimed invention, there was no recognition by Brieaddy that the targeted delivery of an IBAT inhibitor compound to the ileum could provide significant advantages to the patient, nor does Brieaddy

suggest that an IBAT inhibitor could be formulated with a bile acid binder to reduce excess bile acid in the colon. Furthermore, Hirakawa does not suggest or provide a reasonable expectation that IBAT inhibitor compounds could be formulated alone or in combination with a bile acid binder to provide the targeted release of the active agents in the ileum and colon, respectively.

Accordingly, in view of the failure of the cited art to recognize or appreciate the advantages of a targeted release of an IBAT inhibitor in increasing the efficacy of treatment and reduction of side effects, or the optional inclusion of a bile acid binder wherein at least one of the ingredients is formulated in a targeted release formulation, it would not have been obvious to *do* (not obvious to *try*) what Applicants have done. Thus, the direction of Applicants' investigation leading to the claimed invention is clearly not motivated by either Brieaddy or Hirakawa, either alone or in combination.

Furthermore, Hirakawa does not contemplate a pharmaceutical formulation or a method of treatment comprising the administration of one or more active agents as claimed, e.g., an IBAT inhibitor compound and a bile acid binder. The disclosure, Examples and claims of Hirakawa all refer to ***a medicinal active ingredient***. According, there is no suggestion or enabling disclosure of a formulation having the targeted release of two active ingredients of which at least one is formulated in a targeted release, i.e., an IBAT inhibitor released in the ileum and/or a bile acid agent released in the colon. In contrast, the claimed invention includes such pharmaceutical formulations comprising an IBAT inhibitor and a bile acid binder. Therefore, Hirakawa does not provide any motivation to prepare the claimed pharmaceuticals providing the targeted release of an IBAT inhibitor and/or a bile acid binder.

For all of the foregoing reasons, withdrawal of the §103 rejection based on the combination of Brieaddy and Hirakawa is requested.

B. Spielvogel and Hirakawa

Applicants submit that the cited combination of Spielvogel and Hirakawa cannot suggest the claimed invention.

Spielvogel discloses a class of boron-containing compounds which have pharmaceutical applications. The compounds are disclosed to be useful as anti-cancer agents, antiinflammatory agents, hypolipidemic agents, and analgesics (cols. 7-8). The Examiner correctly acknowledges that Spielvogel does not disclose the delivery method, that is, delivery of the IBAT inhibitor compound to the ileum as required by Applicants' claims. Applicants submit that the Examiner's reliance upon Spielvogel for an alleged disclosure of IBAT inhibitor compounds is therefore misplaced.

Although the compounds of Spielvogel are reported to have hypolipidemic properties, there is no teaching that these compounds function as inhibitor compounds of the ileal bile acid transport system of a patient. This particular mode of action of lowering lipids levels is neither disclosed nor suggested by Spielvogel.

The Examiner states that Spielvogel discloses "treatment of intestinal ailments". These ailments are cancers, such as colorectal carcinoma (col. 7, line 59). In contrast, Applicants' invention is directed to treating hyperlipidemia, which refers to a lipid imbalance in the blood, and therefore cannot properly be considered an "intestinal ailment", that is, a disorder which specifically affects a patient's intestinal system.

Moreover, the Examiner incorrectly states that "the compound was tested in the ileum and colon for hypolipidemic activity (Table 2)". Applicants point out that the compounds in Example 13 (to which Table 2 relates) were tested for *cytotoxic activity* in several cell lines, and not in the body for hypolipidemic activity. In this regard, the term "ileum" in Table 2 refers to an

ileum HCT (col. 18, line 44), a human solid tumor line, and the term "colon" refers to a colorectal adenocarcinoma SW480 cell line (col. 18, line 33). Thus, the Example does not show that the compounds were tested in the ileum and colon for hypolipidemic activity, but that cells derived from the ileum and colon were tested for cytotoxicity activity. As such, the Example does not support the Examiner's statements that Spielvogel discloses testing in the ileum and colon for hypolipidemic activity.

Therefore, Spielvogel does not disclose or suggest a pharmaceutical formulation comprising an IBAT inhibitor compound. As acknowledged by the Examiner, Spielvogel does not teach targeted delivery of the IBAT inhibitor compound to the ileum of a patient. Furthermore, Spielvogel does not teach a formulation comprising an IBAT inhibitor and a bile acid binder wherein at least one of these compounds is formulated in a targeted release formulation.

Hirakawa does not overcome Spielvogel's deficiencies in suggesting the claimed invention. As previously discussed in Section IV-A above, Hirakawa discloses a pharmaceutical formulation having targeted delivery in the intestinal tract. The types of active agents which may be used in Hirakawa's invention are disclosed in column 4, lines 24-37. IBAT inhibitor compounds are not disclosed by Hirakawa.

For all the foregoing reasons, withdrawal of the §103 rejection based on the combination of Spielvogel and Hirakawa is respectfully requested.

Applicants bring to the Examiner's attention the Information Disclosure Statements mailed October 23, 2001 and November 27, 2001, which have been received by the PTO and made of record in the file wrapper. Applicants request that the Examiner acknowledge consideration of the documents identified in these Information Disclosure Statements by

providing Applicants with an initialed copy of the Forms PTO-1449 attached to the Information Disclosure Statements.

CONCLUSION

Upon entry of this Amendment, claims 1-10, 15-19, 22, 24-26, and 28-35 are pending. Applicants respectfully submit that claims 1-10, 15-19, 22, 24-26, and 28-35 are in condition for allowance, which action is earnestly solicited.

The Assistant Commissioner is hereby authorized to charge any fee due in connection with this communication to Deposit Account No. 23-1703.

Dated: June 24, 2002

Respectfully submitted,

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Claims 16, 22 and 26-Version With Markings to Show Changes Made:

16. (Twice amended) The [A] pharmaceutical formulation [for simultaneous, separate or sequential administration for the prophylactic or therapeutic treatment of hypercholesterolemia, comprising therapeutically effective amounts of an inhibitor compound of the ileal bile acid transport system of a patient (IBAT inhibitor compound) and] according to any one of claims 1-10, further comprising a bile acid binder.

22. (Twice amended) The [A] method according to claim 15, further comprising administering a therapeutically effective amount of a bile acid binder for the prophylactic or therapeutic treatment of a subject suffering from, or susceptible to, diarrhea during therapy comprising administration of the [an] IBAT inhibitor compound [, comprising administering to the subject a therapeutically effective amount of the pharmaceutical formulation according to any one of claims 16 to 19].

26 (Amended) A method for the prophylaxis or therapeutic treatment of hypercholesterolemia comprising simultaneously, separately or sequentially administering therapeutically effective amounts of a pharmaceutical formulation according to any one of claims 1-10 [an inhibitor compound of the ileal bile acid transport system of a patient (IBAT inhibitor compound)] and a bile acid binder to the patient in need thereof.